original reports abstract

# Understanding Treatment Strategies and Preferences in Nonmetastatic Castration-Resistant Prostate Cancer From the Japanese Physician Perspective

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**PURPOSE** Sixteen percent (16%) of patients with castration-resistant prostate cancer (CRPC) show no bone metastasis at diagnosis. However, 33% will become metastatic within 2 years. The goal of treatment in patients with nonmetastatic CRPC (nmCRPC), therefore, is to delay symptomatic metastases without undue toxicity. With novel antiandrogen treatments of different strengths and limitations available, physician preferences for nmCRPC treatment in Japan should be understood.

**METHODS** A discrete choice experiment was conducted. Physicians chose between two hypothetical treatments in nmCRPC defined by six attributes: risk of fatigue, falls or fracture, cognitive impairment, hypertension, rashes as side effects of treatment, and extension of time until cancer-related pain occurs. Relative preference weights and relative importance were estimated by hierarchical Bayesian logistic regression. Physicians were also asked to make treatment decisions based on four hypothetical patient profiles to understand the most important factors driving decision making.

**RESULTS** A total of 151 physicians completed the survey. Extension of time until cancer-related pain occurs was the most important attribute (relative importance, 32.3%; CI, 31.3% to 33.3%). Based on summed preference weights across all attributes, preferences for hypothetical treatment profiles I, II, and III were compared. A hypothetical treatment profile with better safety though shorter extension time was preferred (I: mean [standard deviation] = 1.7 [1.6 to 2.1]) over treatment profiles with lower safety but longer extension time (II: –2.7 [–2.8 to –2.6] and III: –0.2 [–0.3 to –0.1]). Treatment characteristics were more important factors for physicians' decision making than patient characteristics in prescribing treatment.

**CONCLUSION** Physicians preferred a treatment with better safety profile, and treatment characteristics were the most important factors for decision making. This might have implications in physicians' decision making for nmCRPC treatment in the future in Japan.

**JCO Global Oncol 7:302-310. © 2021 by American Society of Clinical Oncology**



## INTRODUCTION

Castration-resistant prostate cancer (CRPC) presents a spectrum of disease ranging from patients without symptoms or evidence of bone metastases (nonmetastatic castration-resistant prostate cancer [nmCRPC]), but with rising prostate-specific antigen (PSA) levels despite androgen deprivation therapy, to patients with metastases (metastatic CRPC) and significant debilitation because of cancer symptoms.[1] Of the patients with nmCRPC, however, 33% will develop bone metastasis within 2 years.[2] The goal of treatment in patients with nmCRPC, therefore, is to prevent or delay symptomatic metastases without undue toxicity.

In Japan, novel antiandrogens such as apalutamide, enzalutamide, and darolutamide have become available for nmCRPC treatment. These treatment options vary with respect to their effectiveness and safety profile. Enzalutamide was reported to provide extension of the metastasis-free survival (MFS) in patients with nmCRPC (median MFS, 36.6 months *v* 14.7 months [placebo]; hazard ratio [HR], 0.29; $P < .0001$)[3]; furthermore, apalutamide reported extension of MFS in patients with nmCPRC (median MFS, 40.5 months *v* 16.2 months [placebo]; HR, 0.28; $P < .0001$).[4] Both treatment options also reported adverse events (AEs) in the treatment groups including fatigue (30% for apalutamide and 33% for enzalutamide, all grades), rash (24% for apalutamide), falls (16% for apalutamide and 11% for enzalutamide), mental impairment (5% for enzalutamide), and seizures (0.2% for apalutamide and < 1% for enzalutamide, excluding patients with previous history of seizures).[3,4] In 2019, darolutamide was reported to extend MFS in patients with nmCRPC

ASSOCIATED CONTENT

**Data Supplement**

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 23, 2020 and published at ascopubs.org/journal/go on February 22, 2021: DOI https://doi.org/10.1200/GO.20.00358

## CONTEXT

**Key Objective**

Is there a robust understanding on the physician preferences for nonmetastatic castration-resistant prostate cancer (nmCRPC) treatment in Japan?

**Knowledge Generated**

Physicians in Japan considered the efficacy attribute "extension of time until cancer-related pain occurs" as the most important, followed by safety attributes such as risk of falls and fracture, risk of fatigue, and risk of cognitive impairment.

**Relevance**

Given that the recent second-generation androgen receptor inhibitors have shown similar efficacy in terms of metastasis-free survival or overall survival for nmCRPC treatment, safety attributes could potentially influence physician's treatment decision making for patients with nmCRPC in Japan.

(median MFS, 40.4 months *v* 18.4 months [placebo]; HR, 0.41; $P < .001$), with rates of AEs in the treatment group reported to be fatigue (12.1%), rash (2.9%), falls (4.2%), cognitive impairment (0.4%), and seizures (0.2%), including patients with previous history of seizures.[5]

Understanding physician preferences and identifying factors influencing treatment behaviors may help guide current treatment decisions for nmCRPC.[6,7] For example, a previous study has shown that physicians were willing to trade survival to avoid AEs among patients with nonmetastatic prostate cancer (PC), highlighting the importance of managing AEs in the patient population.[8] To date, physician treatment preference studies have particularly been useful for considering both health outcomes and process factors.[9-14]

This study aimed to (1) elicit physician preferences for treatment features or outcomes associated with nmCRPC treatments by means of a discrete choice experiment (DCE), (2) quantify the trade-offs that physicians would be willing to make between efficacy and safety for hypothetical treatments, and (3) identify patient or treatment characteristics associated with a physician's choice of nmCRPC treatment. An important point to note is that throughout this study, efficacy was defined as an extension of cancer-related pain-free interval, rather than overall survival (OS).

## METHODS

### Study Design

This was an observational, cross-sectional study encompassing a series of systematic steps including (1) a literature review to identify the relevant treatment attributes for nmCRPC treatments using PubMed and Embase; (2) the concept-elicitation phase, to elicit concepts for the development of the attributes list for the DCE; (3) a cognitive pretesting phase, to solicit feedback and determine the content validity of the draft DCE questionnaire; and (4) the final DCE online survey. The DCE survey and hypothetical patient profiles were finalized based on feedback from these interviews. The survey was developed in accordance with good research practices,[15] and the protocol was approved by an independent ethics committee in Japan. Informed consent was obtained from all the participants before any activities related to the study.

### Study Population

Physicians recruited in all the three phases met the following inclusion criteria: (1) board-certified physician specializing in urology or oncology, (2) minimum of 5 years clinical practice experience, (3) having treated a minimum of 15 patients with PC in the past 30 days, and (4) able to provide a signed informed consent. There were no specific exclusion criteria. Participating physicians recruited for the concept-elicitation phase were taken from a list of experts identified by the principal investigator and had to have previous experience with novel antiandrogens in clinical trials and daily practice. Participants for the cognitive interview portion were recruited from the same list of experts, without any regard for previous experience with novel antiandrogens. The final online survey was distributed to physicians from the Plamed Asia panel. This panel has more than 45,000 physician members in Japan, with 57% of them working in hospitals with more than 200 beds. For the final online survey, informed consent was obtained directly online before participation. Respondents from all phases could stop participation at any time during the study, for any reason.

A target sample size of 150 physicians who completed the DCE followed the common guidelines[16] and was similar to a majority of previously published studies.[15] This sample size would ensure ± 1%-5% margin of error for the DCE. With six attributes and three levels each, a balanced overlap design resulted in an experimental design of 10 preference-elicitation questions for each physician.

### Statistical Analyses

Physician demographic and clinical practice variables were analyzed descriptively using counts, means, and standard deviations for continuous variables and frequencies and percentages for categorical variables. Internal validity testing of physicians' DCE responses was conducted by assessing the dominance test and whether respondents selected the same medication for all choice questions (no variability). Physicians who failed both checks were excluded.

***DCE analysis.*** In DCE, the choice data were analyzed using a hierarchical Bayesian logistic regression model with effects coding parameterization. The outcome variable of this model was choice, and the predictor variables were the levels within each attribute. Parameter estimates for each attribute level represented the preference weights, which are defined as the marginal utility of a change in that attribute. Parameter estimates for the levels, standard errors, and 95% CIs were reported. Relative importance (RI) estimates were calculated for each attribute, with higher RI weights representing stronger relationships with treatment choice. Mean RI and 95% CIs were reported. To understand physicians' preferences among treatment options with specified attribute levels, for each treatment, the sum of preference weights was calculated for each respondent. The treatment profile with the highest preference weight was the preferred treatment for that respondent. The proportion of physicians who prefer each treatment option was also calculated. Treatment preferences were correlated with demographic and practice-related information to determine whether certain preferences are held more strongly or weakly in some subgroups compared with others.

***Hypothetical patient profile assessment.*** In the patient characteristic assessment, physicians were asked to choose one of the three static treatments that they would prescribe to the given patient profile. A total of four static hypothetical patient profiles were shown to each physician. Multinomial logistic regression models were used to assess the odds ratio and 95% CI between patient characteristics and physicians' treatment choice. The outcome variable was treatment choice, and the predictor variables were the patient characteristics. Patient vignette data enabled quantification of the relative effect of different patient characteristics on physician's choice of nmCRPC treatment. The aspect of the profile (categorized as patient-focused or treatment-focused) that was the most important factor for physicians' treatment decisions was analyzed descriptively.

## RESULTS

### Participants

A total of 151 physicians completed the quantitative DCE survey. A majority of physicians were between 35 and 54 years of age (68.9%) and with an average of 19.7 years of clinical practice experience. One hundred forty-five of them were urologists, and 94 of them received a majority of patients in community or general hospitals.

Physicians were recruited from different regions to ensure geographic distribution and external validity. Physicians on average saw 76.9% of patients with PC, of those an average of 17.1% were patients with CRPC. The details are shown in Table 1.

### Attributes and Levels in the DCE

The specific attributes included in the DCE exercise were (1) risk of fatigue as a side effect of treatment, (2) risk of falls or fractures as a side effect of treatment, (3) risk of cognitive impairment as a side effect of treatment, (4) risk of hypertension as a side effect of treatment, (5) extension of time until cancer-related pain occurs, and (6) risk of rashes as a side effect of treatment (Table 2). The Data Supplement presents an example of a single preference–elicitation question that was presented to respondents.

### Physician Preference Estimates

The full hierarchical Bayesian logistic regression model results are reported in the Data Supplement. All levels of all attributes were significantly associated with choice ($P < .05$). The preference weights and 95% CI are also displayed in Figure 1. The greater the vertical change within an attribute, the stronger the relationship between that attribute and treatment choice.

The RI is further illustrated in Figure 2. Over the range of attributes and levels included in the survey, extension of time until cancer-related pain occurs (RI, 32.28%; 95% CI, 31.29% to 33.27%) was the most important attribute followed by risk of falls or fracture as a side effect of treatment (RI, 18.55%; 95% CI, 16.08% to 21.02%) and risk of fatigue as a side effect of treatment (RI, 16.35%; 95% CI, 15.13% to 17.58%). The risk of cognitive impairment (RI, 12.00%), risk of hypertension (RI, 10.90%), and risk of rashes (RI, 9.92%) as a side effect of treatment were deemed less important compared with the other attributes.

Based on the preference weights for each attribute level, summed preference weights were derived for three hypothetical treatment profiles with varying attribute levels. Treatment profile I had lowest risk of side effects but shorter extension of time until cancer-related pain occurs, whereas treatment profiles II and III had higher risk of side effects but longer extension of time until cancer-related pain occurs.

The mean summed preference weights were 1.695, –2.682, and –0.243 for treatment profile I, profile II, and profile III, respectively. The average preference weights were significantly higher for profile I compared with the other two. One hundred nine of the respondents would prefer profile I, one for profile II, and 47 for profile III based on respondents' summed preference weights (Table 3).

### Subgroup Analysis

Attribute-level preference weights were also analyzed and compared across demographic and clinical practice characteristic variables. No differences were observed. There were only four female physicians and six oncologists, and no statistical inference was made between the relevant subgroups (results not shown).

### Hypothetical Patient Profiles and Treatment Options

Patient profiles were characterized by age, medical history (including comorbidities, history of previous conditions, history of a symptomatic skeletal events, and Gleason score), and current patient status (including Eastern

 

**TABLE 1.** Physician-Reported Demographic and Clinical Practice Characteristics

| Characteristic | Total (N = 151) No. | % |
|---|---|---|
| Sex | | |
| Male | 147 | 97.4 |
| Female | 4 | 2.6 |
| Prefer not to state | 0 | 0.0 |
| Age category, years | | |
| < 35 | 16 | 10.6 |
| 35-44 | 59 | 39.1 |
| 45-54 | 45 | 29.8 |
| 55-64 | 30 | 19.9 |
| ≥ 65 | 1 | 0.7 |
| Prefer not to state | 0 | 0.0 |
| Primary medical specialty | | |
| Urology | 145 | 96.0 |
| Oncology | 6 | 4.0 |
| Place seeing a majority of patients | | |
| Clinic | 13 | 8.6 |
| Community and/or general hospital | 94 | 62.3 |
| Teaching and/or academic hospital | 36 | 23.8 |
| Cancer center | 8 | 5.3 |
| Others | 0 | 0.0 |
| Region of primary practice | | |
| Hokkaido | 8 | 5.3 |
| Tohoku | 11 | 7.3 |
| Chubu | 23 | 15.2 |
| Kanto | 57 | 37.7 |
| Kansai or Kinki | 30 | 19.9 |
| Chugoku | 8 | 5.3 |
| Shikoku | 4 | 2.6 |
| Kyushu (including Okinawa) | 10 | 6.6 |
| Ever prescribed medical treatment options to patients with CRPC | | |
| LHRH analog | 149 | 98.68 |
| Vintage antiandrogen | 148 | 98.01 |
| Novel antihormone abiraterone acetate | 146 | 96.69 |
| Novel antihormone enzalutamide | 147 | 97.35 |
| Chemotherapy | 139 | 92.05 |
| Radiopharmaceutical | 92 | 60.93 |

| | Total (N = 151) Mean | SD |
|---|---|---|
| Years of clinical practice experience, years | 19.7 | 8.1 |
| Number of patients with PC seen in the past 30 days | 76.9 | 88.9 |
| Number of patients with CRPC seen in the past 30 days | 17.1 | 23.9 |
| Number of patients with PC in stages I-III seen in the past 30 days | 52.0 | 58.8 |
| Number of patients with PC in stage IV M0 seen in the past 30 days | 7.9 | 17.3 |
| Number of patients with PC in stage IV M1 seen in the past 30 days | 17.1 | 24.8 |

Abbreviations: CRPC, castration-resistant prostate cancer; LHRH, Luteinizing hormone-releasing hormone; PC, prostate cancer; SD, standard deviation.

Cooperative Oncology Group level, PSA level, PSA doubling time, past treatment use, and patient symptoms). One of the hypothetical patient profiles presented to the physicians is shown in the Data Supplement (details of all four hypothetical patient profiles are given in the Data Supplement). Attribute levels for the three treatment options that physicians chose from are presented in the Data Supplement.

### Patient Characteristics Associated With Physicians' Choice of Treatment

Among the three hypothetical treatment profiles presented to physicians, treatment A had the lowest efficacy (15 months of time to pain extension) and the lowest risk of AEs; in contrast, treatment C had the greatest efficacy but the highest risk of AEs, whereas treatment B was in between. Hypothetical patient profiles I, II, and III had different comorbid conditions, whereas profile IV had no comorbidities. With everything else kept constant, when patients had higher current PSA level, physicians were more likely to prescribe more aggressive treatment over relatively safer treatments. When patients experienced certain comorbid conditions, such as seizure or dementia previously, or had fatigue or depression, physicians were less likely to prescribe more aggressive treatments. Details on the odds ratio and 95% CI can be found in Table 4. In addition, while making treatment decisions, more physicians considered treatment characteristics as the most important factor than patient characteristics (results not shown).

## DISCUSSION

This study provides new insights into the RI that Japanese physicians place on aspects of nmCRPC treatment in Japan. From the physicians' perspective, the efficacy attribute "extension of time until cancer-related pain occurs" and the safety attributes such as risk of falls or fractures as a side-effect of the treatment and risk of fatigue as a side-effect of the treatment were the most important treatment attributes for patients with nmCRPC. A recent study by Srinivas et al[17] assessed the physician's benefit-risk preferences for nmCRPC, and among the safety attributes, physicians were more concerned about cognitive impairment, fractures, and fatigue, which corroborates with the results from this study.

Another study by Srinivas et al[18] reported that patients with nmCRPC and caregivers in the United States preferred treatments that lowered the risk of AEs such as fractures, falls followed by cognitive problems, fatigue, and rash. Additionally, both patients with nmCRPC and caregivers were willing to forego OS to reduce the risk of severity of the AEs.[18] Another study on CRPC patient preference in Japan showed that the patients were more concerned about reduced quality of life (QoL) from the side effects of the treatment rather than extension of survival.[19] Our study found that although physicians were not willing to trade-off

**TABLE 2.** Attributes and Levels Represented in the Discrete Choice Experiment

| Attribute | Levels |
|---|---|
| Risk of fatigue as a side effect of treatment | 15% |
| | 25% |
| | 35% |
| Risk of falls or fractures as a side effect of treatment | 3% |
| | 10% |
| | 20% |
| Risk of cognitive impairment as a side effect of treatment | 0% |
| | 5% |
| | 10% |
| Risk of hypertension as a side effect of treatment | 5% |
| | 15% |
| | 25% |
| Extension of time until cancer-related pain occurs | 15 months |
| | 35 months |
| | 45 months |
| Risk of rashes as a side effect of treatment | 5% |
| | 15% |
| | 25% |

extension of time until cancer-related pain occurs with any single side effect because of treatment, they would do so with multiple lower risks of side effects because of treatment. Furthermore, our study shows Japanese physician's preferences for treatments that show efficacy in pain management and have lower risks for side effects such as fatigue, falls, or fractures. A previous CRPC patient preference study in Japan showed the risk of pain as one of the most important treatment attributes,[19] and our current study shows that physicians value the same attribute highly. These physician preferences are thus aligned with what is currently known about the preferences of Japanese patients with CRPC. However, to better understand the differences and similarities in the nmCRPC treatment preferences among patients with nmCRPC, a similar study with the same attributes could be conducted.

In contrast, however, a recent paper on preferences in nmCRPC revealed that US-based physicians placed more importance on survival than on time-to-pain progression and observed a reduction in cognitive problems from severe to none, a reduction in risk of a serious fracture from 8% to none, and a reduction in fatigue from severe to none as the most important safety attributes.[17] Because survival was not a feature included in our study, the results are difficult to compare; however, of note is that US physicians also placed high value on cognitive impairment in contrast to Japanese physicians.

Furthermore, the preferences in treatment attributes could vary between different cancers. For example, a preference study on melanoma showed that oncology nurses valued OS and AEs equally as most important treatment attributes.[20] Meanwhile, a physician preference study on breast cancer showed that age was also an important factor to make a treatment decision for older patients with breast cancer.[21] Thus, clinical decision making for cancer is complex and estimating the benefits versus the risks of therapies is critically needed for when making treatment decisions for patients.

For patients with PC, QoL has been an important consideration. This is based on a study on long-term survivors of

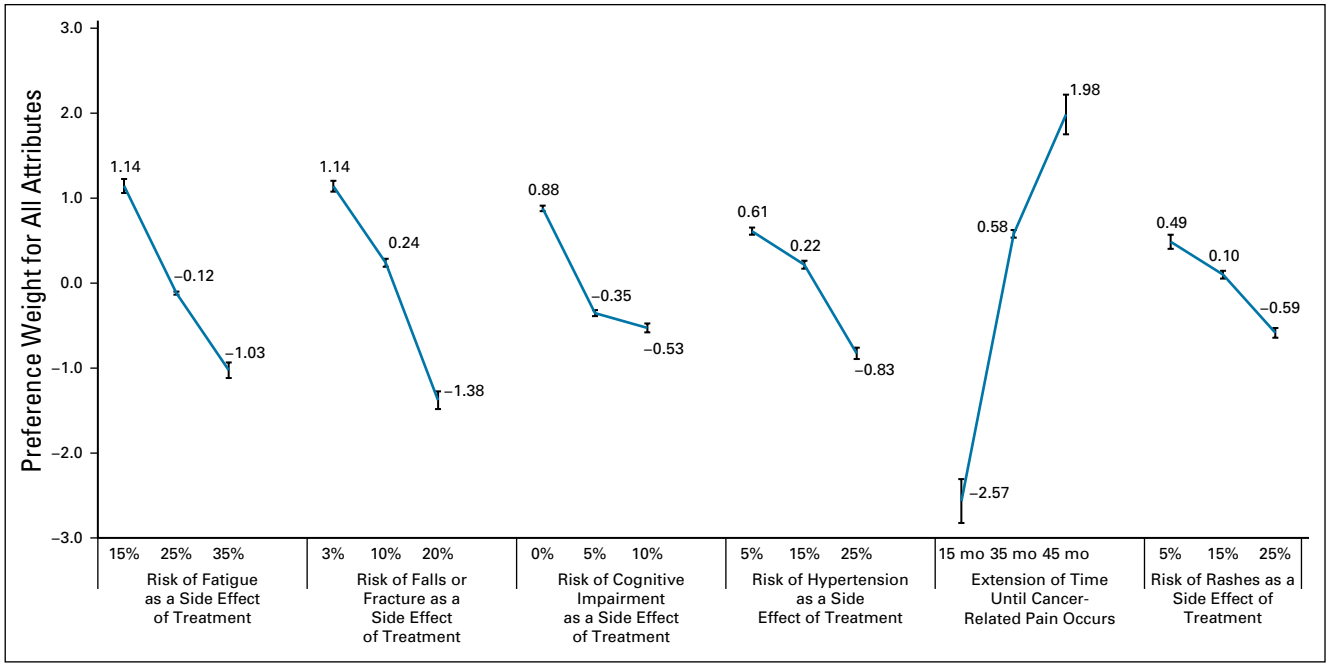


**FIG 1.** Attribute-level preference weights for nmCRPC treatments. mo, months.

 

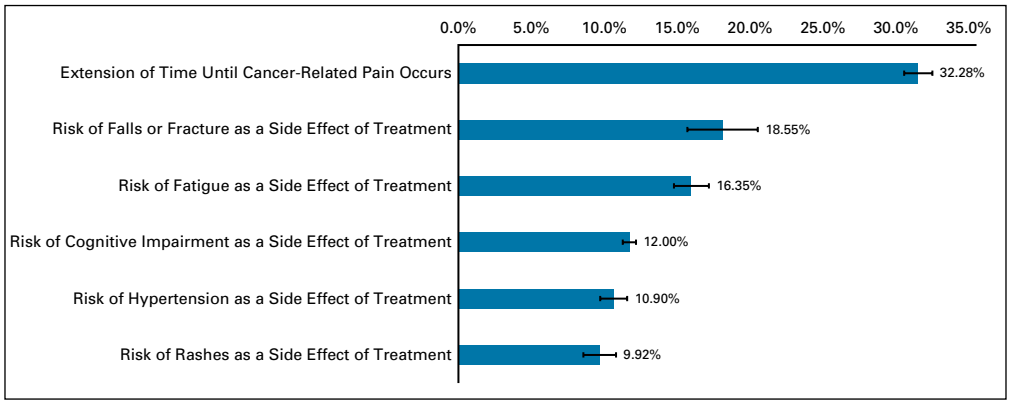


**FIG 2.** Relative importance of nmCRPC treatment attributes among physicians (n = 151).

localized PC, which focused on the regrets patients had with respect to outcomes, and one consistent regret was issues faced on QoL as they recognized that the complications could be permanent.[22] Given the previous literature and current findings on physician's preference of treatment with lesser AEs for patients with complications, this preference of physicians could be potentially associated with addressing unresolved patient needs.

Finally, based on the hypothetical patient profiles, physicians consider specific treatment characteristics as the most important in treatment decision making for nmCRPC. Furthermore, physicians also chose treatment characteristics that have the least possible harm based on the patients' clinical profile and history. Although nmCRPC is a heterogeneous disease,[23] and each patient's treatment should be considered individually, this preference study further highlights the need to closely discern treatment characteristics in decision making.

Overall, this study demonstrates that understanding physician preferences helps to address an important gap to determine the preferences of physicians treating patients with nmCRPC for treatment features or outcomes associated with nmCRPC treatments and unmet needs in Japan.

The data collected in the DCE were based on responses to hypothetical choice profiles. These choices were intended to simulate possible clinical decisions but did not have the same clinical, financial, or emotional consequences of actual decisions. Thus, differences can arise between stated and actual choices. Although attempts were made to rely upon a representative sample of physicians in Japan, there still may be differences in those who participate relative to the general population with respect to treatment practices and patient types they treat and the demographics of the survey participants such as reduced participation of female physicians and oncologists. However, a 2018 report on the current work environment in Japan showed that only 5.3% of practicing urologists were women, which might have been reflected in our study.[24]

In conclusion, this study showed that Japanese physicians treating patients with CRPC place great importance on efficacy attributes such as extension of time until cancer-related pain occurs, followed by attributes that relate to treatment-related AEs. This indicates that physicians place emphasis on balancing patient physiological burden, while aiming to ensure that the treatment works. This also indicates that there is a need to provide a treatment that is both efficacious and with a low risk of side effects to provide the best possible therapeutic option to various patients with nmCRPC. Finally, whether these treatment preferences hold in the real world remains to be seen. Determining

**TABLE 3.** Predicted Choice Shares for Three Hypothetical nmCRPC Treatments With Specified Attribute Levels

| Attributes and Preferences | Treatment Profile I | Treatment Profile II | Treatment Profile III |
|---|---|---|---|
| Attribute levels | | | |
| Risk of fatigue as a side effect of treatment | 15% | 25% | 35% |
| Risk of falls or fracture as a side effect of treatment | 3% | 20% | 10% |
| Risk of cognitive impairment as a side effect of treatment | 0% | 5% | 5% |
| Risk of hypertension as a side effect of treatment | 5% | 25% | 15% |
| Extension of time until cancer-related pain occurs | 15 months | 35 months | 35 months |
| Risk of rashes as a side effect of treatment | 5% | 25% | 15% |
| Summed preference weights, mean (95% CI) | 1.695 (1.350 to 2.040) | −2.682 (−2.796 to −2.568) | −0.243 (−0.348 to −0.138) |
| Physicians in favor of the profile, m (%) | 109 (72.2) | 1 (0.7) | 47 (27.2) |

**TABLE 4.** Odds Ratio of Patient Characteristics Related to Physician Treatment Choice

| | | Treatment B *v* Treatment A | | | Treatment C *v* Treatment A | | |
|---|---|---|---|---|---|---|---|
| **Patient Characteristics** | **Levels** | **Odds Ratio** | **95% CI** | ***P*** | **Odds Ratio** | **95% CI** | ***P*** |
| Age | | 1.013 | 1.003 to 1.022 | .009 | 0.998 | 0.988 to 1.009 | .727 |
| PSA level at diagnosis | | 0.957 | 0.930 to 0.984 | .002 | 0.982 | 0.951 to 1.014 | .259 |
| PSA level current | | 1.044 | 1.008 to 1.082 | .018 | 1.098 | 1.050 to 1.149 | < .001 |
| Gleason score | 7 (4 + 3) | Reference | | | Reference | | |
| | 8 (4 + 4) | 0.925 | 0.826 to 1.036 | .178 | 0.822 | 0.735 to 0.918 | .001 |
| | 9 (4 + 5) | 0.882 | 0.819 to 0.949 | .001 | 0.763 | 0.696 to 0.836 | < .001 |
| | 9 (5 + 4) | 1.181 | 1.038 to 1.345 | .012 | 1.481 | 1.307 to 1.679 | < .001 |
| TNM | T3 | Reference | | | Reference | | |
| | T2 | 0.856 | 0.752 to 0.975 | .019 | 0.691 | 0.610 to 0.782 | < .001 |
| Risk group at diagnosis | High risk | Reference | | | Reference | | |
| | Intermediate risk | 1.049 | 1.019 to 1.081 | .001 | 1.102 | 1.062 to 1.145 | < .001 |
| PSADT current | 10 months | Reference | | | Reference | | |
| | < 10 months | 1.093 | 1.037 to 1.152 | .001 | 1.217 | 1.141 to 1.298 | < .001 |
| Surgery | No | Reference | | | Reference | | |
| | Yes | 1.049 | 1.019 to 1.081 | .001 | 1.102 | 1.062 to 1.145 | < .001 |
| Antiandrogen therapy | No | Reference | | | Reference | | |
| | Yes | 0.925 | 0.885 to 0.968 | < .001 | 0.841 | 0.796 to 0.888 | < .001 |
| ADT (hormone therapy) | No | Reference | | | Reference | | |
| | Yes | 0.925 | 0.885 to 0.968 | .001 | 0.841 | 0.796 to 0.888 | < .001 |
| CAB therapy | No | Reference | | | Reference | | |
| | Yes | 1.093 | 1.037 to 1.152 | .001 | 1.21706 | 1.141 to 1.298 | < .001 |
| Symptoms | No | Reference | | | Reference | | |
| | Fatigue | 1.049 | 1.019 to 1.081 | .001 | 1.102 | 1.062 to 1.145 | < .001 |
| | Fatigue and depression | 0.882 | 0.819 to 0.949 | .001 | 0.763 | 0.696 to 0.836 | < .001 |
| | Frequent urinary | 0.925 | 0.826 to 1.036 | .178 | 0.822 | 0.735 to 0.918 | .001 |
| Complications | No | Reference | | | Reference | | |
| | Seizure | 0.882 | 0.819 to 0.949 | .001 | 0.763 | 0.696 to 0.836 | < .001 |
| | Dementia | 0.925 | 0.826 to 1.036 | .178 | 0.822 | 0.735 to 0.918 | .001 |
| | Fall and hypertension | 1.049 | 1.019 to 1.081 | < .001 | 1.102 | 1.062 to 1.145 | < .001 |

Abbreviations: ADT, androgen deprivation therapy; CAB, combined androgen blockade; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; TNM, tumor (T), nodes (N), and metastases (M).

physician preferences after actual experience in treating patients with available second-generation androgen receptor inhibitors should be considered in the future.

Recent clinical trials of second-generation androgen receptor inhibitors in nmCRPC have shown similar efficacies in terms of MFS and OS, and in addition, some have shown efficacy in extending time-to-pain progression. Furthermore, the results of this preference study emphasize that, after considering efficacy attributes, safety attributes, such as risks of falls or fractures and fatigue, can influence physician treatment decision making in nmCRPC in Japan. Data from these studies and our study could be used in discussing and sharing the profiles of treatment choices with patients, which could lead to aligned physician and patient treatment decision making and better patient care.


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## SUPPORT

Supported by Bayer Yakuhin, Ltd, Kantar, Health Division, received funding from Bayer Yakuhin, Ltd for the conduct of the study and development of the manuscript.

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**Final approval of manuscript:** All authors
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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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**Kazuhiro Suzuki**

**Honoraria:** Bayer Yakuhin, Astellas Pharma, Takeda, AstraZeneca, Daiichi Sankyo, Janssen, Chugai Pharma, Pfizer, Ono Pharmaceutical, MSD, Merck, Nippon Shinyaku
**Consulting or Advisory Role:** Bayer Yakuhin, Takeda, Astellas Pharma, AstraZeneca
**Research Funding:** Takeda, Astellas Pharma, Daiichi Sankyo, Sanofi, Nippon Shinyaku, Kyowa Hakko Kirin, Chugai Pharma

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**Employment:** Kantar Health, Singapore

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**Dianne Athene Ledesma**
**Employment:** Bayer Yakuhin, Ltd

No other potential conflicts of interest were reported.

## ACKNOWLEDGMENT

The authors acknowledge the valuable logistical support for phases I and II provided by Atsuko Matsumoto of Kantar Japan.

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